

T cell immunosurveillance controls B lymphoma development

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We recently showed a critical role for T cells in the immunosurveillance of nascent B cell lymphomas arising from mutations impacting plasma cell differentiation. Our data suggest that CD8⁺ T cells continuously eliminate mutated B cells that fail to downregulate their co-stimulatory machinery and the Fas death receptor, thus constraining B lymphoma pathogenesis.

Diffuse Large B Cell Lymphoma (DLBCL) is the most frequent type of non-Hodgkin lymphoma in adults and, despite improved treatment, remains fatal for half the patients afflicted with this disease.¹ Alterations of certain genes, including loss of function of the tumor suppressor *PRDM1/Blimp1* or deregulated expression of the oncogene *BCL6*, are thought to cause a large proportion of DLBCL cases. While Bcl6 is essential for germinal center (GC) B cell formation, the transcription factor Blimp1 is a negative regulator of GC fate but indispensable for the differentiation of B cells to plasma cells.^{2,3}

In our recent work, we have demonstrated that T cells are essential for the immunosurveillance of nascent B cell lymphoma.⁴ In this study, Blimp1-deficiency or overexpression of Bcl6 in the B cell lineage led to an accumulation of pre-plasmablastic B cells, which represent a transient stage during normal plasma cell differentiation.³ In agreement with earlier reports,^{5,6} mutations in either gene resulted in only slow and infrequent development of lymphoma, suggesting that mutations in Blimp1 or Bcl6 alone are not sufficient for disease development. Strikingly, removal of T cells resulted in the rapid development of DLBCL-like lymphoma, which could be eradicated by polyclonal CD8⁺ T cells in a manner dependent on Fas ligand and co-stimulation through

CD28. Thus, malignant transformation of mature B cells required both mutations that impaired intrinsic differentiation processes and escape from constant T cell-mediated tumor surveillance.⁴

DLBCL arises from GC B-cells or their precursors, activated B cells. GCs are unique sites where antigen-stimulated B cells with the help of CD4⁺ T cells undergo massive proliferation, somatic hypermutation, and class switch recombination, eventually producing high affinity, long-lived plasma cells and memory B cells (Fig. 1). GC B cells and their immediate precursors express the enzyme activation induced cytidine deaminase (AID), which catalyzes mutations in the immunoglobulin loci required for affinity maturation and class switching. The expression of AID, however, also leads to potentially harmful mutations of other genes, including oncogenes such as *BCL6*, or chromosomal alterations such as *c-myc/IgH* translocations.⁷ Thus, during immune responses, B cells are highly susceptible to DNA damage and transformation. Yet, despite oncogenic mutations in normal activated B cells of healthy individuals, lymphoma development is rare. While this reflects the requirement for multiple oncogenic changes for transformation, it is also consistent with the hypothesis that the immune system can recognize and eradicate transformed B cells, thereby

inhibiting cancer development. Immune deficiencies, treatment with immunosuppressive drugs, or acquisition of additional mutations, may promote progression of B cell lymphoma and other malignancies.⁸ In support of this notion, the majority of DLBCL cases show mutations that lead to loss or misexpression of MHC class I, or alternatively, exhibit other mutations that affect immune surveillance including those impacting the functional expression of MHC class II, CD58 or the immune checkpoint molecule PD-L1 (CD274).⁹ Overall these data strongly suggest that escape from immune control plays a central role in DLBCL development. This was supported by a study that showed that the Epstein-Barr virus-derived antigen LMP1, expressed under the control of B cell specific regulatory elements, can directly activate T-cell mediated immune surveillance.¹⁰ Our study, however, for the first time provided direct evidence for a central role of T cells in preventing the development of spontaneous lymphoma triggered by mutations blocking intrinsic cellular differentiation pathways not associated with the expression of a foreign antigen.

Our work also provided direct confirmation for the important roles of co-stimulation and Fas/Fas-ligand interactions in the control of B cell lymphoma.⁴ Fas and the costimulatory molecules CD80 and CD86 are not expressed on resting

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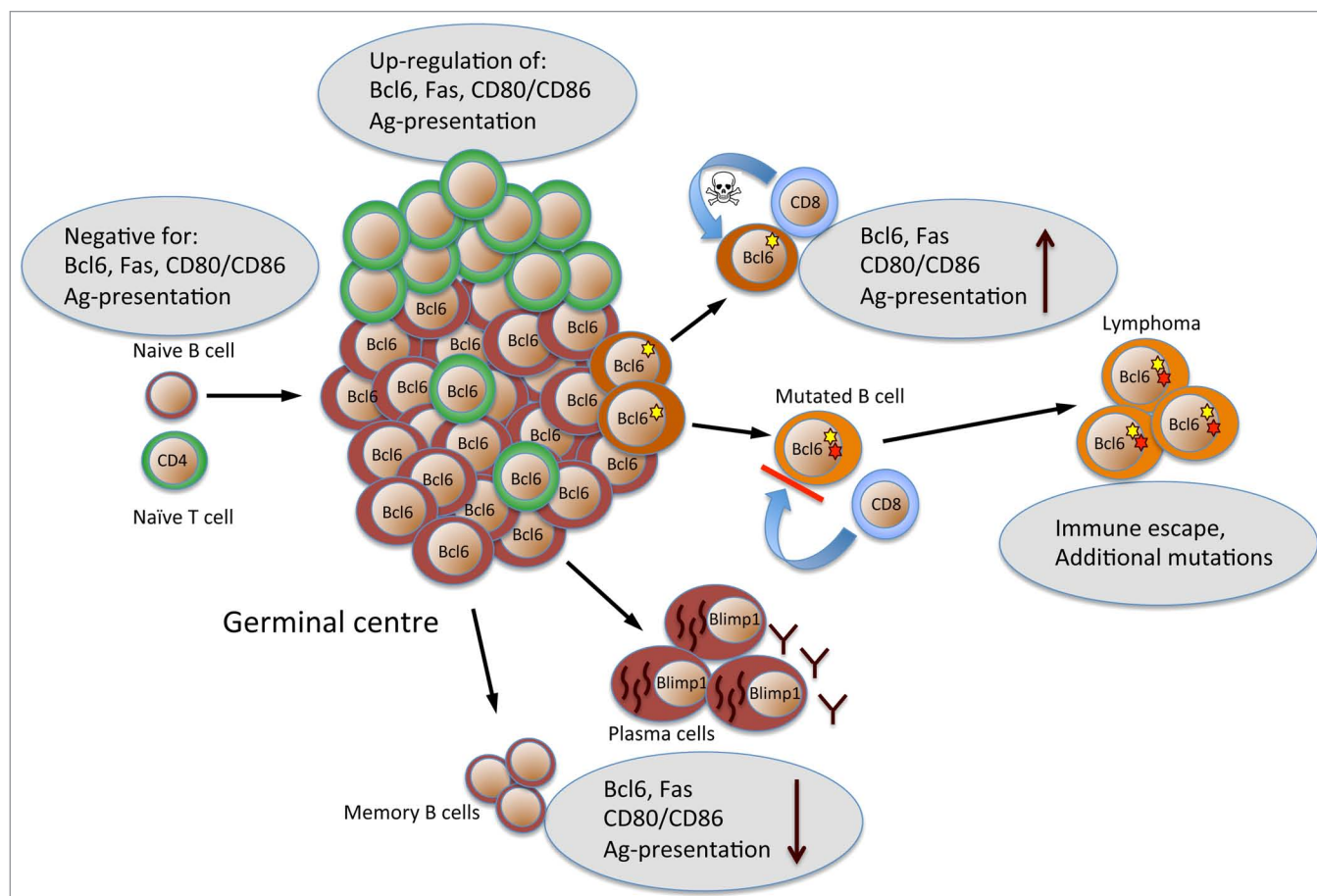


Figure 1. Immune surveillance of B cells during the germinal center (GC) response. Naïve B cells after antigen-activation upregulate expression of the transcription factor Bcl6, the enzyme activation induced cytidine deaminase (AID), the death receptor Fas, and the costimulatory molecules CD80 and CD86 as part of the germinal center program. At the same time B cells acquire the ability to efficiently present foreign and self-antigen (Ag). Bcl6⁺ GC B cells with the help of CD4⁺ T cells undergo clonal population expansion as well as AID-mediated somatic hypermutation and class switch recombination. This produces not only affinity matured long-lived plasma cells and memory B cells but also B cells carrying potentially deleterious mutations (marked by an asterisk). If the cells maintain high expression of Fas and costimulatory molecules, they are marked for destructions by CD8⁺ T cells. Additional mutations, however, can lead to immune escape and the outgrowth of B cell lymphoma.

B cells but upregulated during B cell activation. Their expression is high on GC B cells but downmodulated upon exit from the GC during memory B cell development or Blimp1-mediated plasma cell differentiation. Our data demonstrate that Fas and co-stimulatory molecules remain expressed on B lymphoma cells in the absence of T cell mediated immune control but are preferentially lost during lymphoma development in T cell sufficient mice. This suggests that failure to downregulate these molecules “marks” potentially harmful B cells outside of the GC. From this arises a model in which pre-malignant B cells, generated through the activity of AID during normal B-cell responses, are continuously eradicated by T cells, while mutations that block such

surveillance promote tumor development (Fig. 1). While our work shows that this process is critical for preventing lymphoma development, the precise contribution of CD4⁺ and CD8⁺ T cells to this process remains uncertain. CD8⁺ T cells were best equipped to eradicate existing malignant cells in a lymphoma transfer model utilized in our study. However, CD4⁺ T cells may provide critical help to CD8⁺ T cells in the initial stages of lymphoma prevention. Furthermore, it is unclear whether, and how, immune surveillance impacts the outcome of normal B-cell responses.

Another interesting conceptual implication of our study is that T cell-mediated immunosurveillance is not necessarily driven by antigens exclusively expressed by lymphoma B cells. Instead our data

support a model, in which T cells bearing T-cell receptors for self-antigens with avidity below the threshold of negative thymic selection, have the capacity to eliminate potentially malignant B cells that are identified based on their elevated expression of MHC molecules presenting self-peptides in conjunction with high levels of co-stimulatory molecules. This process of T cell-mediated immune surveillance of activated B cells may have evolved as a mechanism to deal with the potentially dangerous consequences of AID-mediated off-target mutations during class switch recombination and somatic mutation in humoral immune responses.

Importantly, our data imply that pre-malignant B cells can be identified based on their phenotype. Thus, it may be

feasible to target these cells precautionarily in order to prevent lymphoma development. Such a strategy may be beneficial in individuals at risk of developing B cell lymphoma, such as patients under long-term immunosuppressive drug regimens or individuals with lymphoproliferative disorders.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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